Knowledge of fractional exhaled nitric oxide use among doctors working in a local respiratory department

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ABSTRACT

INTRODUCTION The aim of this survey is to assess the knowledge regarding fractional exhaled nitric oxide (FeNO) testing among our junior and senior physicians currently working within the respiratory department.

METHODS All medical doctors above foundation level working in the respiratory department for at least 3 months at Mater Dei Hospital were asked to complete a questionnaire with a total of 19 true or false questions. Questions were based on current international guidelines and recommendations.

RESULTS Our cohort included a total of 25 doctors. The mean age of experience working as a physician was 8 years; 84% of doctors (n=21) were aware that FeNO testing is available at our hospital. Questions assessing clinical indications and interpretation of FeNO in asthma and different respiratory conditions showed overall significantly better results between junior and senior trainees (p=0.013), though still lacking in certain aspects especially in conditions unrelated to asthma.

CONCLUSIONS Our results show that doctors working in our department are overall knowledgeable about the use of FeNO in relation to the diagnosis and management of asthma. However, its use and interpretation in relation to other respiratory conditions and co-morbidities is lacking. This emphasizes the need to educate local respiratory trainees further on FeNO testing.

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KEYWORDS

asthma, nitric oxide, FeNO, fractional, exhaled

Received: 24 October 2022
Revised: 5 December 2022
Accepted: 18 December 2022

INTRODUCTION

Asthma is a clinical diagnosis characterized by the presence of airway hyper-responsiveness and re-modelling with reversible airway obstruction. The diagnosis of asthma may be occasionally challenging. Common symptoms such as shortness of breath, wheezing and cough are relatively non-specific and found in other conditions and diseases. Various investigations including lung function tests and bronchoprovocation challenges may be used by clinicians to aid diagnosis. More recently, fractional exhaled nitric oxide (FeNO) has been added to the list of investigations that clinicians may use to diagnose asthma, aid in the selection of treatment options, and monitor the response to therapy[1].

FeNO is measured by exhaling into an analyzer and has been found to be elevated in patients with atopic asthma[1]. It has been recently made available in our hospital center for the diagnosis and monitoring of asthmatic patients. The aim of this survey is to assess the knowledge regarding FeNO testing among our junior and senior medical trainees and specialists within the respiratory department two years since its availability, to ensure that our trainees are making proper use of this relatively new available service within our hospital and to further help continuous medical education.

METHODS

Malta is a small Mediterranean country within the European Union, which has only one acute state hospital, Mater Dei Hospital (MDH), catering for most services, with one of the specialties being respiratory medicine.

A questionnaire was devised based on guidelines from the European Respiratory Society (ERS), British Thoracic Society (BTS) and the Global Initiative for Asthma (GINA), and from a literature review carried on PubMed with specific keywords. The questionnaire included demographic data, years of experience and duration working in the respiratory department. The questionnaire had a total of 19 true/false questions and was divided into 3 sections; general information regarding FeNO, factors affecting FeNO levels, and respiratory conditions that may alter FeNO levels.

All medical doctors above foundation level working in the respiratory department for at least 3 months at Mater Dei Hospital were asked to complete a questionnaire. A cut-off of <12 months and ≥12 months working in our respiratory department was set to check whether there is a statistical significance in the knowledge of FeNO testing amongst these two categories. The participants working in the department for <12 months are junior trainees currently rotating in the

Pneumon 2023;36(1):4
https://doi.org/10.18332/pne/157588

respiratory department whilst in their core medical training. However, trainees working in the department for ≥12 months are those trainees that have completed their core medical training and are currently in their respiratory specialty training.

The questionnaire was kept anonymous and once completed by the participants, it was placed in a closed box to ensure anonymity. The participants completed the questionnaire in the presence of the investigator to avoid participants searching for the correct answers. In addition, once completed, an information booklet regarding FeNO was given to the participants which included answers to all the questions in the questionnaire. Results were compiled and analyzed. Statistical analysis was performed using Microsoft Excel.

RESULTS

Our cohort included a total of 25 doctors working in the respiratory department who agreed to participate in the analysis. Only one doctor refused to participate and hence was not included in this study.

The majority of doctors were male (n=14; 56%); 76% (n=19) of participants were aged <35 years, with 11 of them aged <30 years. There were no doctors aged >50 years. The mean age of experience working as a medical professional was 8 years.

In total, 84% of doctors (n=21) were aware that FeNO testing is available at Mater Dei Hospital. Of these, 61.9% had been working in the respiratory field for ≥12 months, whilst 38.1% for <12 months.

Table 1 represents the questionnaire and the respective answers. Table 2 shows the number of participants who answered the question correctly, incorrectly, or failed to answer (n=25). Table 3 shows the number of correct answers divided according to experience working in the respiratory department (<12 months or ≥12 months).

When comparing the results in Table 3 between the younger junior doctors and the more experienced trainees, one can immediately appreciate that the senior doctors were significantly more likely to answer correctly (p=0.013), which signifies that there is a statistical significance between junior and senior trainees. In questions 5–9, which assessed mostly clinical knowledge regarding FeNO testing, the doctors working in the respiratory department for ≥1 year had overall better results, with three of these mentioned questions having a 100% correct response rate. The next section of the questionnaire assessed factors affecting FeNO level,

Table 1. Questionnaire with the respective answers

No.	Question	Answer
1	Nitric oxide is produced in the lungs	True
2	FeNO testing is required before progressing to asthma treatment	False
3	The use of FeNO is strongly recommended in monitoring airway inflammation in patients with eosinophilic asthma	True
4	FeNO testing is used for non-eosinophilic asthma	False
5	FeNO testing is used to assess potential response to anti-inflammatory agents, notably inhaled corticosteroids	True
6	A negative test excludes a diagnosis of asthma	False
7	FeNO level >40 ppb in adults is considered a positive test	True
8	FeNO level <25 ppb means a less likelihood of eosinophilic inflammation and responsiveness to corticosteroids	True
9	High FeNO level >50 ppb can help identify poor adherence in asthma patients with otherwise seemingly 'controlled' asthma	True
10	Males and tall individuals tend to have a low FeNO level	False
11	Diet high in nitrates may cause a high FeNO level	True
12	Patients with active rhinovirus infection may cause a low FeNO level	False
13	Patients recently treated with inhaled or oral corticosteroids may have a low FeNO level	True
14	Cystic fibrosis causes a low level of FeNO	True
15	Smoking effects FeNO level	True
16	Pulmonary hypertension causes a raised FeNO level	False
17	High FeNO levels are noted in atopic non-eosinophilic bronchitis	False
18	High FeNO levels are found in COPD exacerbation	True
19	FeNO testing can be used in post-COVID follow-up	False

Table 2. Number of participants who answered the question correctly, incorrectly, or failed to answer (N=25)

No.	Question	Answered correctly n (%)	Answered incorrectly n (%)	Did not answer the question n (%)
1	Nitric oxide produced in the lungs	16 (64)	6 (24)	3 (12)
2	FeNO testing is required before progressing to asthma treatment	25 (100)	0	0
3	The use of FeNO is strongly recommended in monitoring airway inflammation in patients with eosinophilic asthma	16 (64)	8 (32)	1 (4)
4	FeNO testing is used for non-eosinophilic asthma	19 (76)	6 (24)	0
5	FeNO testing is used to assess potential response to anti-inflammatory agents, notably inhaled corticosteroids	23 (92)	2 (8)	0
6	A negative test excludes a diagnosis of asthma	25 (100)	0	0
7	FeNO level >40 ppb in adults is considered a positive test	21 (84)	4 (16)	0
8	FeNO level <25 ppb means a less likelihood of eosinophilic inflammation and responsiveness to corticosteroids	20 (80)	5 (20)	0
9	High FeNO level >50 ppb can help identify poor adherence in asthma patients with otherwise seemingly 'controlled' asthma	25 (100)	0	0
10	Males and tall individuals tend to have a low FeNO level	13 (52)	11 (44)	1 (4)
11	Diet high in nitrates may cause a high FeNO level	14 (56)	11 (44)	0
12	Patients with active rhinovirus infection may cause a low FeNO level	16 (64)	7 (28)	2 (8)
13	Patients recently treated with inhaled or oral corticosteroids may have a low FeNO level	20 (80)	4 (16)	1 (4)
14	Cystic fibrosis causes a low level of FeNO	12 (48)	12 (48)	1 (4)
15	Smoking effects FeNO level	21 (84)	4 (16)	0
16	Pulmonary hypertension causes a raised FeNO level	21 (84)	3 (12)	1 (4)
17	High FeNO levels are noted in atopic non-eosinophilic bronchitis	14 (56)	10 (40)	1 (4)
18	High FeNO levels are found in COPD exacerbation	11 (44)	14 (56)	0
19	FeNO testing can be used in post-COVID follow-up	16 (64)	9 (36)	0

Table 3. Number of correct answers divided according to experience working in the respiratory department (N=25)

No.	Question	<12 months n (%) correct	≥12 months n (%) correct
1	Nitric oxide produced in the lungs	5 (41.6)	11 (84.6)
2	FeNO testing is required before progressing to asthma treatment	12 (100)	13 (100)
3	The use of FeNO is strongly recommended in monitoring airway inflammation in patients with eosinophilic asthma	7 (58.3)	9 (69.2)
4	FeNO testing is used for non-eosinophilic asthma	10 (83.3)	9 (69.2)
5	FeNO testing is used to assess potential response to anti-inflammatory agents, notably inhaled corticosteroids	10 (83.3)	13 (100)
6	A negative test excludes a diagnosis of asthma	12 (100)	13 (100)

Continued

Table 3. Continued

No.	Question	<12 months n (%) correct	≥12 months n (%) correct
7	FeNO level >40 ppb in adults is considered a positive test	11 (91.6)	10 (76.9)
8	FeNO level <25 ppb means a less likelihood of eosinophilic inflammation and responsiveness to corticosteroids	8 (66.6)	12 (92.3)
9	High FeNO level >50 ppb can help identify poor adherence in asthma patients with otherwise seemingly 'controlled' asthma	12 (100)	13 (100)
10	Males and tall individuals tend to have a low FeNO level	6 (50)	7 (53.8)
11	Diet high in nitrates may cause high FeNO level	7 (58.3)	7 (53.8)
12	Patients with active rhinovirus infection may cause a low FeNO level	8 (66.6)	8 (61.5)
13	Patients recently treated with inhaled or oral corticosteroids may have a low FeNO level	7 (58.3)	13 (100)
14	Cystic fibrosis causes a low level of FeNO	6 (50)	6 (46.1)
15	Smoking effects FeNO level	10 (83.3)	11 (84.6)
16	Pulmonary hypertension causes raised FeNO level	9 (75)	12 (92.3)
17	High FeNO levels are noted in atopic non-eosinophilic bronchitis	8 (66.6)	6 (46.1)
18	High FeNO levels are found in COPD exacerbation	5 (41.6)	6 (46.1)
19	FeNO testing can be used in post-COVID follow-up	5 (41.6)	11 (84.6)

and in questions 10–12 there was a similar response rate between junior and senior trainees, although question 13 had a 100% correct response rate amongst the senior doctors. In the final part of the questionnaire, there was an overall better correct response rate amongst the senior doctors except for question 17, as can be seen in Table 3.

DISCUSSION

Asthma is a disease affecting more than 350 million people worldwide. Assessing a patient with suspected asthma requires a thorough history including possible exposure to any allergens and occupational exposure, examination and a combination of investigations such as blood investigations, imaging, lung function tests and possibly FeNO measurement in order to assess the phenotype of the condition and hence provide optimal treatment[2].

The pathophysiological process of asthma is mostly secondary to type-2 (T2) inflammation which tends to be associated with allergic and/or eosinophilic asthma. This usually responds to inhaled or systemic corticosteroids, and ultimately targeted by biological therapies if the patient does not respond to initial inhaler therapy. T2 inflammation is driven by enhanced interleukin-4 (IL-4), IL-5 and IL-13 cytokine production. This results in eosinophilic inflammation, goblet cell hyperplasia, airway hyper-responsiveness, and immunoglobulin E (IgE) production. In addition, IL-13 induces nitric oxide synthase in bronchial epithelium[2,3].

Nitric oxide is a gaseous molecule found in the respiratory and cardiovascular systems and is a modulator of type 2 inflammation with increased levels in expiration of many asthmatics. FeNO can be regarded as an indirect marker of IL-13-mediated type 2 airway inflammation and is the only licensed point-of-care test available for type 2 inflammation in asthma[3,4]. Most junior trainees were not knowledgeable about the physiology of nitric oxide, and only 41.6% (n=5) of participants with <1 year of experience in respiratory medicine answered the first question correctly. Most senior doctors responded correctly.

Patients suspected of suffering from asthma, in whom the diagnosis is not established based on the initial spirometry combined with bronchodilator reversibility testing, the European Respiratory Society (ERS), British Thoracic Society (BTS) and the Global Initiative for Asthma (GINA) suggest measuring FeNO as part of the diagnostic work-up in adults aged >18 years with suspected asthma[5-7].

An elevated FeNO level reflects the allergic airway inflammation in asthmatic patients and may be correlated with treatment response. Truong-Thanh et al.[8] state that in asthma patients with a high FeNO level, a higher dose of inhaled corticosteroids (ICS) may be needed to achieve a better response. A literature search did not reveal any additional information to support or refuse this. Nearly all the participants were aware that FeNO measurement can be used to assess treatment response and monitoring. Only two participants with <1 year experience in respiratory medicine answered this question incorrectly.

A normal FeNO level does not exclude asthma, and FeNO testing is not entirely required to proceed to asthma treatment. As per the ERS guidelines, a cut-off value of 40 parts per billion (ppb) offers the best compromise between

sensitivity and specificity while a cut-off of 50 ppb has a high specificity (>90%) and is supportive of a diagnosis of asthma. A FeNO value <40 ppb does not rule out asthma and similarly high FeNO levels themselves do not define asthma. High levels of FeNO (≥50 ppb) can result from undertreatment, poor inhaler technique or incompliance to treatment. In contrast, low levels of FeNO (≤25 ppb) could suggest that the inflammation is being adequately controlled. Alternatively, low FeNO values can suggest the absence of corticosteroid-sensitive type 2 inflammation or a misdiagnosis of asthma[6,9]. The participants had an overall correct response rate with respect to questions tackling the above knowledge across the junior and senior trainees.

FeNO levels might be altered by several external factors or other respiratory conditions as stated in the BTS guidelines. Cigarette smoking has been shown to reduce FeNO levels, and the extent of the reduction varies according to cigarette consumption. However, FeNO is still raised in smokers with asthma, compared to smokers without asthma. Most participants answered this respective question in the questionnaire correctly. Only four participants from the whole cohort replied incorrectly[7,10].

FeNO level increases with the consumption of nitrate rich foods. In addition, other determinants to FeNO measurement include rhinovirus infection which increases FeNO level secondary to the increased upregulation of nitric oxide synthase expression. In COPD exacerbations, patients have been found to have elevated FeNO levels. Furthermore, patients with cystic fibrosis (CF) have normal or lower FeNO levels. These three important points were highlighted in several questions with similar results between junior and senior trainees, as can be seen in Table 3[7,10,11].

In our literature review, two follow-up studies were found which examined exhaled nitric oxide exchange in patients with pulmonary hypertension (PH). One of these studies compared the measurements of ten patients with PH with those of 12 controls. FeNO was found to be lower in the PH group, and FeNO levels increased to the level of controls after PH treatment[12,13].

It is important to highlight a particular study regarding FeNO and COVID-19. The nature of the inflammatory and fibrotic processes found in patients with post-COVID-19 syndrome made it possible to speculate that FeNO can be a useful biomarker. In this study, none of post-COVID patients had bronchial asthma or was being treated with a corticosteroid. Only 19 out of 68 post-COVID-19 patients reported a FeNO value >25 ppb. The data generated in this study suggested that measurement of FeNO is not useful as a biomarker in post-COVID-19 patients. The final question of the questionnaire tackled this study with most experienced trainees responding correctly with a correct response rate of 84.6% (n=11)[14].

Limitations

An inevitable limitation of this study is the small sample size. As mentioned above, Malta has only one state hospital which provides all the training for the up-and-coming medical practitioners in their respective specialities. Another limitation is that junior physicians allocated in the respiratory department as part of their core medical training, are not provided with an induction course/meeting to inform them of all the services the respiratory department provides. Hence this might have been a limitation when answering the questionnaire. This can be easily corrected administratively with an induction meeting and the set-up of tutorials or lectures to these junior trainees at the start of their rotation. Senior doctors on the other hand, through their training, conferences, webinars, seminars, lectures and exit exams have an exposure to such knowledge.

CONCLUSIONS

This survey was carried out to assess the knowledge on FeNO use and interpretation to indirectly help with continuous medical education and postgraduate learning. Our results show that doctors working in our department are overall knowledgeable about the use of FeNO in relation to the diagnosis and management of asthma. However, its use and interpretation in relation to other respiratory conditions and co-morbidities is lacking.

The results, as expected, showed that more senior doctors have overall more knowledge regarding FeNO; however, there are still some areas which one can improve upon. Further intra-departmental audits, studies and educational meetings are recommended to further improve clinical expertise and optimize further the management of our patients.

CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

FUNDING

There was no source of funding for this research.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval was not required for this study, according to the University of Malta. Completion of the survey questionnaire was deemed informed consent.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

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